REMARKS

In view of the following Remarks, the Examiner is requested to withdraw the rejection and allow Claims 1, 5-8, 13, 17, 28, 30 and 32, the only claims pending and currently under examination in this application.

FORMAL MATTERS:

Claims 31 and 33 are cancelled without prejudice.

Claims 30 and 32 are amended to correct grammar.

No new matter is added. As such, the Examiner is requested to enter the above amendments.

INTERVIEW SUMMARY:

Applicants thank Examiner Shen for the courtesy of conducting an in-person interview on December 8, 2010 with Applicants' representative Bret Field to discuss the Rejection under 35 U.S.C. §112, first paragraph for enablement set forth in the Office Action. The Examiner further explained to the Applicants' representative that the rejection was based upon the belief that making mutant fluorescent proteins that emit in colors other than the wild type fluorescent protein was not possible, and that making mutant fluorescent proteins with 90% identity, i.e. comprising 23 mutations, that retain fluorescence was not predictable. Applicants' representative pointed to the working examples provided in the specification of mutants of SEQ ID NO:10 that fluoresced in colors other than yellow (the color emitted by the subject nucleic acid, SEQ ID NO:10). In addition, Applicants' representative provided examples of mutants of GFP and dsRED that fluoresce in a multitude of colors other than that of their respective parent proteins. Finally, the Applicants' representative pointed to the many examples in the art of teachings of fluorescent protein structure and fluorescent protein mutants as evidence of how well-understood the structure of fluorescent proteins was and how to mutate those fluorescent proteins without destroying that structure at the time of filing the present application. The Examiner indicated that Applicants' arguments appeared reasonable and would be considered in overcoming the rejection, and suggested that Applicants provide a summary highlighting the main points of these arguments at the start of the response to this rejection. Applicants have done so below.

In addition, the Examiner requested that claim 31 be canceled, because it may be interpreted as broadening the scope of the pending claims, and that claim 33 be canceled,

because it is redundant with claim 1. In an effort to expedite prosecution and without agreeing to the correctness of these statements, Applicants have canceled these claims herein.

Executive Summary

Pending claim 1 recites "an isolated nucleic acid molecule encoding a fluorescent protein, wherein said protein has at least 90% identity with full length SEQ ID NO: 10."

Applicants will demonstrate herein that:

- The art provides a multitude of examples of mutants of GFP and dsRED that fluoresce in a multitude of colors other than that of their respective parent proteins. See the discussion at page 10, lines 19-24 below regarding GFP mutants that emit in blue, cyan and yellow, and at page 11, lines 1-5 below regarding the dsRed mutants mHoneydew, mBanana, mOrange, dTomato, tdTomato, mTangerine, mStrawberry, mCherry, Plum and Raspberry that emit in the colors embodied by their names. See also the discussion at page 12, lines 18-30 of how the fluorophore is mutated to arrive at these colors.
- The instant specification provides working examples of mutants of SEQ ID NO:10 that fluoresce in colors other than yellow, the color of SEQ ID NO:10. See the discussion at page 13, lines 15-17 and page 12, lines 30-34 below regarding mutants M1G1 and M1C1, which emit in green and cyan, respectively, and how they are made by mutating the fluorophore.
- The art provides a wealth of teachings on the importance of the β-can and fluorophore structures to fluorescent proteins, and provides a wealth of teachings on how that structure is readily identifiable across proteins with as little as 26% sequence identity conserved between them, e.g. GFP and dsRED. The art provides a plethora of examples of mutations that may be made throughout these fluorescent proteins, including in the fluorophore itself, to yield mutant proteins that retain fluorescence activity. See the discussion of these mutants below at page 9, lines 7-31 page 10, line 16 – page 11, line 5.
- The instant specification provides multiple working examples of mutations that may be made throughout the length of SEQ ID NO:10 that maintain fluorescence. See the discussion of these mutants below at page 13, lines 9 – 19.

Thus, the specification in view of the art provides sufficient guidance and working examples that one of ordinary skill in the art would have been able to make and use fluorescent proteins having at least 90% identity with full length SEQ ID NO:10, i.e. mutants comprising mutations in 23 residues, including fluorescent proteins that emit in colors other than yellow, without undue experimentation. As such, the pending claims are enabled.

REJECTIONS UNDER §112, ¶1 - ENABLEMENT

Claims 1, 5-8, 13, 17, 28, and 30-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule encoding a yellow fluorescent protein, wherein said protein has at least 96% identity with full length SEQ ID NO: 10, and a vector/cell/kit comprising an isolated nucleic acid molecule encoding a yellow fluorescent protein, wherein said protein has at least 96% identity with full length SEQ ID NO: 10, does not allegedly reasonably provide enablement for (1) said isolated nucleic acid molecule encodes any fluorescent protein other than a yellow fluorescent protein, wherein said protein has at least 96% identity with full length SEQ ID NO: 10, or (2) any vector/cell/kit comprising said isolated nucleic acid molecule encodes any fluorescent protein other than a yellow fluorescent protein, wherein said protein has at least 96% identity with full length SEQ ID NO: 10.

With respect to enablement, courts have held that: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.,* 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

In making this rejection, the Examiner asserts on page 11, lines 9-15 that: "phiYFP shares only about 50% identity with well characterized GFP (from jelly fish), and there is no evidence on the record supporting that the amino acid residue required for exhibiting green fluorescence for GFP can be directly applied to the aligned corresponding amino acid residues present in phiYFP. Therefore, it would require undue experimentation for an artisan to determine which amino acids are necessary and sufficient for phiYFP-M1 (i.e. the claimed SEQ ID No. 10) to be a yellow fluorescent protein to support the breadth of the claims".

Applicants respectfully submit that the pending claims do not require that the nucleic acid encode a *yellow* fluorescent protein; rather, they simply require that the encoded protein be fluorescent. Applicants submit that, in view of the well-developed state of the art regarding the structure of fluorescent proteins and the high level of predictability in the art for making mutants

of those fluorescent proteins that fluoresce in a multitude of colors at the time of filing of the present application, the present specification provides sufficient guidance and working example that one of ordinary skill in the art would be able to make and use nucleic acids encoding fluorescent proteins of any color with at least 90% identity to full length SEQ ID NO:10 without undue experimentation.

State of the art and level and predictability in the art of fluorescent proteins

The specification teaches that the knowledge in the art regarding the structural elements that provide for the fluorescence of GFP and dsRED are relevant to the knowledge of how the structure of phiYFP provides for phiYFP's fluorescence and the fluorescence of its mutants. At the time of filing the present application, the structure of fluorescent proteins and its relevance to the fluorescence of GFP was well known; see, for example, Yang et al. ((1996) Nat. Biotech 14:1246-51) (of the record) and Ormo et al. ((1996) Science 273:1392-95) (of the record), and the review of the field by Tsien et al. ((1998) Ann Review Biochem 6767:509-544) (Exhibit A) For example, Yang et al. teaches that GFP forms a β-can with a fluorophore at its center (Fig. 1), teaches which residues comprise each β-strand sheet of the β-can (Fig. 3), teaches that the fluorophore consists of residues 65-67 (page 1246, column 2, lines 1-6), teaches which residues elsewhere in the protein interact with the fluorophore environment and thus will be most likely to impact its fluorescence if mutated (Figures 4 and 5, Table 1, and page 1248, column 2, last paragraph – page 1249, full column 1), and references other teachings in which these and other residues have been systematically explored to determine their impact on fluorescence (reference 22). Likewise, the relevance of this structure to other fluorescent proteins was also well established; see, for example, Matz et al. ((1999) Nat Biotech 17:969-973) (of the record) and the review of the field by Matz et al. ((2002) Bioessays 24:953-959) (of the record). Finally, the importance of particular residues to the particular color in which the proteins fluoresce was also well established; see, for example, Sample et al. ((2009) Chem Soc Rev. 38(10):2852-64), pages 2855-2859) (of the record), which provides a post-filing review at pages 2855-2859 of the state of this particular art at the time of filing the present application. Thus, Applicants submits that the state of the art with regard to the crystal structure of chromo- or fluorescent proteins and the relevance of that structure to their color/fluorescence function was well developed and highly predictable at the time of filing of the present application.

In addition, making mutants of chromo- or fluorescent proteins that maintain the structures required for fluorescence was highly predictable. For example, as exemplified in

Matz et al. ((1999) Nat Biotech 17:969-973) (of the record), it was well understood in the art at the time of filing of the present application that the amino acid residues that are conserved across homologous proteins most likely have a critical role in maintaining the structure and function of those homologous proteins, and furthermore, that conserving these residues when generating mutants will ensure that the mutants will fold properly. Moreover, it was also well understood in the art that to identify such conserved residues, one need only compare the sequences of the homologous proteins by aligning them using well-developed programs known in the art, e.g. ClustalW or BLAST. As such, the art at the time of filing of the present application was replete with reports of rationally-designed mutants of fluorescent proteins that retain fluorescence but that, in some instances, fluoresce in a color different from that of the parent protein.

For example:

- Siemering et al. ((1996) Current Biol. 6(12):1653-63) (of the record) teaches seven mutants of GFP (mgfpA, mgfpB, mgfp4, mgfp5, mgfp4 + Y66H, mgfpA + Y66H).
- Yang et al. ((1998) J Biol Chem 273(14):8212-8216) (of the record) teaches two mutants of GFP.
- Heim et al. ((1996) Current Biol. 6:178-182) (of the record) teaches 2 mutants of GFP that emit green (S65T, P4-1), 2 mutants of GFP that emit blue (P4, P4-3) and 2 mutants of GFP that emit cyan (W7, W2) (Table 1).
- Ormo et al. ((1996) Science 273:1392-95) (of the record) teaches 3 mutants of GFP (T203H/S65T, T203U/S65T, T203U/F64L/S65G/S72A, and T203Y/S65G/V68L/S72A) of GFP that emit yellow (Table 2)

Importantly, there is an abundance of evidence that indicates that this high degree of predictability extends beyond GFP to other types of fluorescent proteins. For example:

- Bevis et al. ((2002) Nat. Biotechnol 20(1):83-7) (of the record) teaches 7 mutants of dsRed (N42H, N42Q, DsRed1, dsRed2, DsRed.T1, DsRed.T3, DsRed.T4; see page 83, col. 2, para. 3-4, page 84, Table 1).
- Campbell et al. ((2002) PNAS 99(12):7877-82) (of the record) teaches 4 mutants of dsRed (I125R, dimer2, tdimer2, mRFP1; see paragraph bridging pages 7878-9, and Table 1).

- Shaner et al. ((2004) Nat Biotechnol 22(12):1567-72) (of the record) teaches 8 mutants of dsRed (mHoneydew, mBanana, mOrange, dTomato, tdTomato, mTangerine, mStrawberry, and mCherry).
- Wang et al. ((2004) P.N.A.S. 101(48): 16745-16749) (Exhibit B) teaches 2 mutants of dsRed (Plum and Raspberry).

It is noted that, as demonstrated by the alignment of dsRED to GFP below, dsRED shares only 26% identity with GFP:

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Query = GFP
Subject = dsRED
Length=225

 Score = 55.1 bits (131),  Expect = 1e-12, Method: Compositional matrix adjust.
 Identities = 55/218 (26%), Positives = 103/218 (48%), Gaps = 13/218 (5%)

Query  16   VELDGDVNGHKFSVSGEGEGDATYGKLTLKFICTT-GKLPVPWPTLVTTFSYGVQCFSRY  74
            V ++G VNGH+F + GEGEG    G  T+K   T  G LP  W  L   F YG + + ++
Sbjct  16   VRMEGTVNGHEFEIEGEGEGRPYEGHNTVKLKVTKGGPLPFAWDILSPQFQYGSKVYVKH  75

Query  75   PDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDG  134
            P  +   D+ K + PEG+  ER + F+D G      +   +    + +++  G++F  DG
Sbjct  76   PADIP--DYKKLSFPEGFKWERVMNFEDGGVVTVTQDSSLQDGCFIYKVKFIGVNFPSDG  133

Query  135  NILGHK-LEYNYNSHNVYIMADKQKNGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPV  193
             ++  K + +  ++  +Y      K  I    K++    DG   L +   ++  +  PV
Sbjct  134  FVMQKKTMGWEASTERLYPRDGVLKGEIHKALKLK----DGGHYLVEF--KSIYMAKKPV  187

Query  194  LLPDNHYLSTQSALSKDPNEKRDHMVLLEFVTAAGITH  231
              LP  +Y+ ++  ++   +   D+ ++ ++    G  H
Sbjct  188  QLPGYYYVDSKLDIT---SHNEDYTIVEQYERTEGRHH  222
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However, as evidenced by the references by Bevis, Campbell, Shaner and Wang, even this low % identity was sufficient to enable the ordinarily skilled artisan to identify amino acids that could be mutated in the dsRED sequence so as to generate the aforementioned 21 mutants, all of which retain fluorescence activity but, in some instances, emit in different fluorescence spectra. Accordingly, it must be said that there existed a high degree of predictability in the art with regard to making mutants of fluorescent proteins with at least 90% identity to the parent sequence that retain the ability to fluoresce, be it in the emission spectrum of the parent protein or another spectrum.

Thus, the Applicants submit that, at the time of filing of the present application, the state of the art with regard to the relationship between the structure of chromo- or fluorescent proteins

and their ability to fluoresce was well developed, and the art of generating mutants of chromo- or fluorescent proteins that maintain their overall structure and fluorescence while sometimes fluorescing in colors other than the color of the parent protein was highly predictable.

Guidance and working examples provided

Applicants submit that, in view of the well developed state of the art and high degree of predictability in the art discussed above, the specification provides more than sufficient guidance and working examples on how to make and use the nucleic acids encoding fluorescent proteins with at least 90% identity to full length SEQ ID NO:10 without undue experimentation.

The specification discloses, for the first time, the sequence of phiYFP and mutants thereof. The specification teaches the relevance of the relationship between the structure and fluorescence of GFP and Anthozoan fluorescent proteins to the relationship between the structure and fluorescence of the disclosed proteins (p. 1, l. 13-26; Figure 1), which, as discussed above, would be sufficient information to guide the ordinarily skilled artisan in predicting which amino acids could be mutated to retain fluorescence while, if desired, modulating the color of that fluorescence. For example, the art teaches that the fluorophore of GFP comprises residues Ser^{65}, Tyr^{66} and Gly^{67} (Ormo et al., p. 1392, col. 1, l. 19-23), and that by mutating residues 65 and/or 66 and, in some instances, other residues that contribute to the fluorophore environment, one can produce GFP mutants that emit in colors other than green (Ormo et al., Table 1; Heim et al. p. 178, col. 1, l. 16-22, and Table 1). Likewise, the art teaches that the fluorophore of dsRed comprises residues Gln^{66}, Tyr^{67} and Gly^{68} (Shaner et al. p. 1, paragraph bridging cols. 1 and 2, and that by mutating the dsRed residues corresponding to residues Ser^{65} and/or Tyr^{66} of GFP (Gln^{66} and Tyr^{67} of dsRed), and, in some instances, other residues that contribute to the fluorophore environment, one can produce dsRed mutants that emit at colors other than red (Shaner et al., p. 3, col. 1, l. 9-16, p. 4, col. 1, l. 5 – 18). Finally, the present specification teaches in the alignment of Figure 1 that phiYFP residues Thr^{65}, Tyr^{66}, and Gly^{67} correspond to the residues of the GFP fluorophore; thus, the ordinarily skilled artisan would know that these residues make up the fluorophore of phiYFP. Furthermore, the specification provides examples of mutants of phiYFP–M1G1 and M1C1, discussed below—to demonstrate that by mutating the Thr^{65} and other residues that contribute to the fluorophore environment, one can produce phiYFP mutants that emit in colors other than wild type phiYFP and phiYFP mutants in which the Thr^{65} is conserved.

Furthermore, the specification teaches methods of confirming the aforementioned predictions, by teaching methods of making mutant nucleic acids encoding mutant proteins (p. 8, l. 21-p. 9, l. 9; see also p. 26, l. 8-11), and of testing these mutant nucleic acid, for example by transfecting the nucleic acids into cells in culture, waiting 20 hours, and imaging the cells on a fluorescence microscope (p. 29, l. 7-16). Thus, the specification provides sufficient guidance that one of ordinary skill in the art would know how to design a multitude of other nucleic acid sequences that encode fluorescent proteins encompassed by the pending claims.

In addition, the specification teaches 7 working examples of nucleic acids that encode proteins with at least 90% identity to full length SEQ ID NO:10. These include wild type phiYFP (SEQ ID NO:1, encoding SEQ ID NO:2) as well as phiYFP mutants Y1 (SEQ ID NO:3, encoding SEQ ID NO:4), M0 (SEQ ID NO:5, encoding SEQ ID NO:6), M1 (SEQ ID NO:7, encoding SEQ ID NO: 8), M1 humanized (SEQ ID NO:9, encoding SEQ ID NO: 10), M1G1 (SEQ ID NO:17, encoding SEQ ID NO:18), and M1C1 (SEQ ID NO:19, encoding SEQ ID NO:20) (p. 25, l. 5 – p. 27, l. 10). Applicants note that two of these mutants—M1G1 and M1C1–retain fluorescence upon mutation but emit in a different color (M1G1 fluoresces in the green spectrum, and M1C1 fluoresces in the cyan spectrum). Accordingly, the specification provides precedence for producing fluorescent proteins with at least 90% identity to full length SEQ ID NO:10 that are *not* yellow fluorescent proteins.

Thus, Applicants maintain that the specification in view of the art provides a reasonable amount of guidance and working examples on the relationship between the structure of the disclosed proteins and their function as fluorescent molecules that one of ordinary skill in the art would be able to identify other species of the claimed genus without undue experimentation.

In attempting to establish this rejection, the Examiner at page 11, lines 17-21 cites Shagin et al. for teaching that "homologs of the green fluorescent protein (GFP), including the recently described GFP-like domains of certain extracellular matrix proteins in Bilaterian organisms, are remarkably similar at the protein structure level, yet they often perform totally unrelated functions, thereby warranting recognition as a superfamily."

Applicants respectfully submit that Shagin et al., in fact, supports the Applicants' assertions of the predictability in the art of fluorescent proteins with regard to the relationship

between structure and function and the predictions that may be made based upon this relationship. Shagin et al. teaches a class of proteins from bilateral organisms called G2FP proteins that have a GFP-like domain but that are not fluorescent or colored (instead, they serve as protein-binding modules that participate in control of the extracellular matrix formation during development) (abstract, l. 1-3, and p. 842, col. 1, l. 29-34). Shagin et al. teaches that the G2FP proteins should be considered structural homologs of GFP because they share the GFP-like "beta-can" fold domain (p. 844, col. 2, l. 26-29). However, no mention is made of conservation of a fluorophore domain, a three-amino acid domain which, as discussed above, is known in the art (see, e.g. Matz et al.) to be necessary for fluorescence. Furthermore, Hopf et al., which is cited by Shagin et al. as the art that first demonstrating this conservation of the β-can domain between the G2FP proteins from bilateral organisms and the GFP family of fluorescent proteins, also teaches no fluorophore; rather, Hopf et al. teaches that the G2FP protein under study ("Nidogen") comprises an EGF domain and a beta-can domain. See, for example, the abstract, provided below:

Nidogen, an invariant component of basement membranes, is a multifunctional protein that interacts with most other major basement membrane proteins. Here, we report the crystal structure of the mouse nidogen-1 G2 fragment, which contains binding sites for collagen IV and perlecan. The structure is composed of an EGF-like domain and an 11-stranded β-barrel with a central helix. The β-barrel domain has unexpected similarity to green fluorescent protein. A large surface patch on the β-barrel is strikingly conserved in all metazoan nidogens. Site-directed mutagenesis demonstrates that the conserved residues are involved in perlecan binding.

Thus, the teachings of Shagin et al. are consistent with what one of ordinary skill in the art would already know from the art, namely, the importance of the fluorophore and the amino acids that comprise it, and which amino acids should be conserved when varying the sequence in a given fluorescent protein so as to not affect its function as a fluorescent protein. Accordingly, and contrary to the Examiner's assertions, Shagin et al. actually demonstrates the predictability in the art of fluorescent proteins with regard to the structures known to be important for fluorescence and this necessary to conserve when mutating the protein to retain fluorescence, namely, a β-can structure and a fluorophore, which the specification teaches are comprised by proteins of the present application.

In attempting to establish this rejection, the Examiner at page 12, lines 1-4 cites Sample et al. for teaching "FP family members generate their chromophores autocatalytically through a series of posttranslational modifications. The fluorescence characteristics of GFP-family members are influenced in important ways by the local microenvironment surrounding the chromophore."

Applicants respectfully submit that Sample et al., too, supports the Applicants' assertions of the predictability in the art of fluorescent proteins with regard to the relationship between structure and function and the predictions that may be made based upon this relationship. As indicated by the Examiner, Sample et al. does teach that the fluorescence characteristics of GFP-family members are influenced in important ways by the local microenvironment surrounding the chromophore. However, Sample et al. then provides *four pages* of teachings (see pages 2855-2859) of mutations that may be made in GFP that provide for fluorescence in spectrums other than green. Thus, like Shaner et al. (discussed above), which teaches mutations that can be made in dsRED that provide for fluorescence in spectrums other than green, Sample, in fact, support the Applicants' position that nucleic acids encoding fluorescent proteins with at least 90% identity to SEQ ID NO:10 that are not yellow fluorescent proteins is fully enabled.

In attempting to establish this rejection, the Examiner on page 12, lines 14-15 cites Parmley et al. for teaching that "alterations in either protein folding or translational efficiency could result in changed protein functions encoded by synonymous mutations".

Applicants respectfully submit that Parmley et al. relates to the general field of protein structure and function. In contrast, and as discussed above, the field of fluorescent proteins is well-developed. In view of the wealth of working examples in the specification and the art of mutations that can be made to fluorescent proteins that retain fluorescence, it must be expected that effects of synonymous mutations as taught by Parmley et al. on this class of proteins are minimal at best. As such, Applicants maintain that, even in view of Parmley, it must be said that making mutant fluorescent proteins that retain fluorescence, be it in the spectrum of the parent protein or a different spectrum, is highly predictable.

Thus, Applicants maintain that, in view of the well developed state of the art and high level of predictability in the art with regard to making mutant fluorescent proteins that fluoresce in the color of the parent protein as well as in other colors, the specification provides sufficient guidance and working examples to make and use the nucleic acid molecules of the pending claims without undue experimentation. As such, the pending claims are sufficiently enabled.

In view of these remarks, reconsideration and withdrawal of the rejection is requested.

OBJECTIONS TO THE CLAIMS

Claims 30-33 are objected to because: 1) the limitation "claim 1" in claims 31-33 should read "claim 1", and 2) to improve the clarity of claims 30 and 32, the phrase "having a nucleotide sequence—" should be replaced by a wherein clause.

Applicants have amended claims 30 and 32 as suggested by the Examiner, and have canceled claim 31. Accordingly, this objection may be withdrawn.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number EURE-006.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

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Enclosure(s): Exhibit A: Tsien (1998) Ann Review Biochem 6767:509-544
Exhibit B: Wang et al. (2004) P.N.A.S. 101(48): 16745-16749

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